REMARKS

Claims 1-36 are pending in the present application. Claims 1, 3, 5-8, 8-10, 18, 19, 21, 23-28 and 36 have been amended. Claims 2 and 20 have been canceled. Support for the amendments to Claims 1, 3, 5-8, 8-10, 18, 19, 21, 23-28 and 36 is found throughout the specification. Specifically, support for the amendments to claims 1 and 19 is found at page 10, lines 13-21. Support for the amendments to claims 3 and 21 is found at page 10, lines 15-17. Claims 18 and 36 are amended to remove an unnecessary acronym. The rest of the amendments change the dependencies or antecedent bases of the claims without introducing new matter. Accordingly, Applicant respectfully submits that the amendments to claims 1, 3, 5-8, 8-10, 18, 19, 21, 23-28 and 36 are fully supported by the specification as filed.

Claim Objections

Claims 18 and 36 were objected to for inclusion of a parenthetical in the claims. Claims 18 and 36 have been amended to remove the parenthetical and the enclosed word. Reconsideration and withdrawal of the objections to claims 18 and 36 are therefore respectfully requested.

Rejection of claims under 35 U.S.C. § 112

Claims 1, 3-4, 11-19, 21-22, and 29-36 were rejected under 35 U.S.C. § 112, first paragraph, for failure of the specification to enable the invention as claimed for purine analogs or for derivatives of azathioprine or purines broadly. The claims are amended to specifically state that the methods of the claimed invention comprises administration of a formulation consisting essentially of azathioprine, 6-mercaptopurine, 6-thioguanine, or a pharmaceutically acceptable salt thereof.

Applicant respectfully submits that the instant specification is enabling for the use of azathioprine, 6-mercaptopurine, 6-thioguanine, or a pharmaceutically acceptable salts thereof in the claimed methods, particularly in view of the teachings of the instant specification at page 10, lines 15-21. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 1, 3-4, 11-19, 21-22, and 29-36 under 35 U.S.C. § 112, first paragraph.

Claims 1, 5-10, and 23-28 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The basis for the rejection of claim 1 was not given. 37 CFR §1.104 and MPEP 707.07 require that the Office Action be complete and clear. MPEP 707.07(d) states that for any claim rejected on the merits, the ground of rejection must be fully and clearly stated. MPEP 707.07(i) states that in every letter, each pending claim should be mentioned by number and its treatment or status given. Applicant considered the grounds for the rejections of claims 5-10 and 23-28 under 35 U.S.C. § 112, second paragraph , but claim 1 does not appear to suffer from the defects identified in these claims. Applicant respectfully requests that the basis for the rejection of claim 1 under 35 U.S.C. § 112, second paragraph be fully and clearly stated by the Examiner, or that the rejection of claim 1 under 35 U.S.C. § 112, second paragraph be withdrawn.

Claims 9-10 and 27-28 were rejected for use of the limitation "said effective amount of azathioprine" without sufficient antecedent basis. Claims 5-8, 10, 23-26 and 28 were rejected for use of the limitation "said azathioprine" without sufficient antecedent basis. Due to the amendments to claims 1 and 19, antecedent basis for this limitation is now present. Specifically, claims 5-7 and 10 are amended to depend from claim 3, which provides antecedent basis for "said azathioprine". Claim 8 replaces "azathioprine" with "formulation", which has antecedent basis in the claim from which it depends. Likewise, Claims 23-25 and 28 are amended to depend from claim 21, which

recites "said azathioprine". Claim 26 replaces "azathioprine" with "formulation", which has antecedent basis in the claim from which it depends. By these amendments, antecedent basis for the cited terms is now present for each of these claims. Accordingly, reconsideration and withdrawal of the rejections of claims 5-10 and 23-28 under 35 U.S.C. § 112, second paragraph for lack of antecedent basis is respectfully requested.

Claims 8 and 26 were rejected for inclusion of the term "quick", which was stated to be indefinite because one of skill in the art would not be able to determined the time period described by the term. The rejection is respectfully traversed. Applicant points out that the term is not used in isolation, but is part of the term "quick dissolving tablet". This term is well known to those of skill in the art to denote a particular type of oral medicine delivery formulation that dissolves in the patient's mouth on the order of seconds, rather than minutes to provide immediate conversion of the medicine from a solid to a soluble form. The term "quick-dissolving" denotes a particular class of formulations and not any specific time period, as suggested in the Office Action. Because the term describes a class of formulations well known to those in the art, no further description or limitation is necessary for the skilled artisan to be apprised of the scope of the claim. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 8 and 26 under 35 U.S.C. § 112, second paragraph.

Rejections of Claims under 35 U.S.C. § 103(a)

Claims 1-36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lozada in view of WO 97/31921 (Qi et al.). The rejections are respectfully traversed.

The Office Action states that Lozada teaches a method of treating patients with chronic inflammatory mucocutaneous disease that comprises administering azathioprine along with a

steroidal antiinflammatory agent. Qi et al. is relied upon to teach treatment of oral lesions associated with autoimmune disorders with azathioprine; and the use of various formulation alternatives.

A *prima facie* case of obviousness requires a showing of motivation to combine the references in the manner asserted by the Examiner. MPEP § 2142. The Examiner may look to the prior art or to the knowledge of one of skill in the art, but may not look to the applicant's disclosure to find the necessary motivation. MPEP § 2142. It is insufficient to show that the references can be combined; the prior art must also suggest the desirability of the combination. MPEP § 2143.01; *in re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *in re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999); *in re Kotzab*, 55 USPQ2d 1313 (Fed. Cir. 2000). Furthermore, the references must be considered in their entirety, i.e., as a whole, including portions that would lead away from the claimed invention. MPEP § 2141.02.

In addition to the requirement for a showing of motivation to combine the references as suggested, a *prima facie* case also requires a showing of a reasonable expectation of success. MPEP § 2143.02; *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *In re Tomlinson,*363 F.2d 928, 150 USPQ 623 (CCPA 1966). Finally, a *prima facie* case also requires all the claim limitations be taught or suggested by the prior art. MPEP §2143.03.

Claims 1 and 19, and the claims dependent thereon, have been amended to clarify that the methods of the present invention are directed to treatment or prevention of an autoimmune disease of the mouth, by topical administration of a formulation that consists essentially of an effective amount of azathioprine, 6-mercaptopurine, 6-thioguanine nucleotide or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier. The use of the term "consists essentially of" limits the scope of a claim to the specified steps and those additional steps that do not materially affect the basic and novel characteristics of the claimed invention. MPEP 2111.03. The basic and

novel characteristic of the present invention is a method for treating or preventing an autoimmune disease of the mouth that includes the steps of applying to the mouth of a patient an amount of azathioprine or a derivative thereof effective to accomplish alleviation or reduction of symptoms. These characteristics are described in the instant specification at page 9, lines 6-14, and further at page 14, lines 1-4. The azathioprine or a derivative thereof is contacted with the mouth of the patient for a period of at least one minute, and thereafter expectorated or swallowed. This method provides for a higher local concentration of the immunosuppressive agent than would be possible by the conventional systemic administration route. In addition, such topical administration minimizes the significant undesirable side-effects associated with systemic exposure to azathioprine (see below).

It is known in the art that systemically administered azathioprine alone is undesirable for treatment of autoimmune conditions because of its potentially severe side effects, which include potential blood abnormalities (especially leukopenia), low WBC count, and possible increased cancer risk (page 259, col. 1). In addition, azathioprine is known to induce myelosuppression, hypersensitivity, mild gastrointestinal reactions, and adverse drug interactions (see A. Anstey and J.T. Lear, *Azathioprine: Clinical Pharmacology and Current Indications in Autoimmune Disorders*, BioDrugs 1998, 9(1):33-47, at pages 36, 37-39; A. Winkelstein, *The Effects of Azathioprine and 6-MP on Immunity*, J. Immunopharmacology 1979 1(4):429-454, pages 445-446, both already of record in this application). Oral administration of azathioprine is overwhelmingly favored over intravenous administration, because the intravenous preparation of azathioprine is an extreme irritant (see Anstey and Lear, page 35, first column).

Lozada teaches that systemically-administered azathioprine in combination with prednisone acts synergistically in the treatment of chronic inflammatory mucocutaneous diseases (page 257, col.

1; page 258, col. 2). To achieve the instant invention as presently claimed, the teachings of Lozada et al. would have to be drastically modified. One would first have to remove the prednisone component, and then reformulate the azathioprine, usually administered in the form of a tablet, into a format suitable for topical administration. Removal of the prednisone would mean loss of what the cited reference itself calls one of the most effective drugs for treatment of chronic inflammatory mucocutaneous diseases (Lozada, page 257, first column). Supplying azathioprine in a format suitable for topical administration is further undesirable to one of skill in the art, because azathioprine in solution is known to be an extreme irritant. Nothing in the references cited in the Office Action provides the high level of motivation required to modify these teachings so drastically. In fact, Lozada and the rest of the prior art teaches the opposite. Lozada teaches that a beneficial synergistic effect is obtained when predisone is combined with azathioprine. Moreover, Lozada and the prior art illustrate the significant risks and adverse side-effects that accompany the use of systemically administered azathioprine would discourage one of skill in the art from making such modifications.

Lozada
has prednisone

Nothing in Qi et al. provides motivation to modify the references either. The Office Action does not rely on Qi et al. for anything more than to show that azathioprine may be included in immunosuppressive compounds, and the different formulations of compositions used in treating autoimmune disorders. Qi et al. is concerned with the use of triptolide analogs in the treatment of autoimmune disorders. Qi et al. mentions azathioprine only as a drug optionally coadministered with the triptolide analogs (page 19, lines 3-12 – "In the potentiated immunosuppressant therapy method of the invention, a triptolide analog of Formula 1 above *may be administered with an immunosuppressant drug* together in the same formulation, or separately in separate formulations...The immunosuppressive drug *which is administered with the triptolide analog* is

preferably one of the following:...(c) azathioprine,..."). Nothing in Qi et al. provides any motivation at all for one of skill in the art to consider administering azathioprine alone, in the absence of the triptolide analogs taught by the specification. Even less does Qi et al. provide any motivation to employ a topically useful formulation of azathioprine without the triptolide analogs disclosed therein, which form the basis for the teachings of this reference. Consequently, Qi et al. provides even less of a teaching for the use of azathioprine by itself in autoimmune diseases than Lozada.

Nothing in either Lozada or Qi et al. provides sufficient motivation to make the drastic modifications to the teachings of those references that would be necessary to arrive at the invention as presently claimed. Applicant respectfully submits that the invention as claimed in claims 1, 3-19, and 21-36 is patentable. Accordingly, Applicant respectfully requests reconsideration and allowance of claims 1, 3-19, and 21-36.

No extension of time fee pursuant to 37 C.F.R. §1.136(a) or any other fee is believed to be required in this response to the March 28, 2001 Office Action. However, should a fee for submission and entry of this amendment be deemed to be required, the Commissioner is authorized and requested to charge any amounts due on account of the present submission, including extension of time fees, to the Deposit Account of the undersigned attorneys, which is: **Deposit Account No. 12-2475**.

Should the Examiner have any further comments or questions, or believe that certain actions would expedite the issuance of the present application, the Examiner is invited to telephone the Applicant's representative at the number listed below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE TO CLAIMS

1. (Amended) A method for treating an autoimmune disease of the mouth, comprising topically contacting the mouth of a patient in need of such treatment with a formulation consisting essentially of an effective amount of [a purine analog or a pharmaceutical salt thereof] azathioprine, 6-mercaptopurine, 6-thioguanine nucleotide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

3. (Amended) The method of Claim 1, wherein said [purine analog is] formulation includes azathioprine or a [derivative] pharmaceutically acceptable salt thereof.

5. (Amended) The method of Claim [1] 3, wherein said azathioprine or a pharmaceutically acceptable salt thereof is in a solution or suspension at a concentration between 0.5 and 50 mg/ml.

6. (Amended) The method of Claim [1] 3, wherein said azathioprine or a pharmaceutically acceptable salt thereof is administered at a dosage between 50 and 250 mg/day.

7. (Amended) The method of Claim [1] 3, wherein said azathioprine or a pharmaceutically acceptable salt thereof is administered in a solution or a suspension.

8. (Amended) The method of Claim 1, wherein said formulation [azathioprine or a pharmaceutically acceptable salt thereof] is administered in the form of a member selected from the group consisting of a lozenge, a lollipop, a pellet, a cream, a gel, an ointment, a quick dissolving tablet, gum, or a mucosal adhesive.

9. (Amended) The method of claim 1, wherein said step of topically contacting includes rinsing the mouth of said patient with said [effective amount of azathioprine or a pharmaceutically acceptable salt thereof] formulation for at least one minute; and

swallowing said [effective amount] formulation after said step of rinsing.

10. (Amended) The method of claim 1, wherein said step of topically contacting includes rinsing said mouth with said [effective amount of azathioprine or a pharmaceutically acceptable salt thereof] formulation for at least one minute, and thereafter expectorating said [azathioprine] formulation without swallowing.

18. (Amended) The method of claim 1, wherein said autoimmune disease of the mouth is lichenoid changes and aphthae associated with acquired immune deficiency syndrome ((AIDS)).

19. (Amended) A method for preventing an autoimmune disease of the mouth, comprising topically contacting the mouth of a patient in need of such treatment with a formulation consisting essentially of an effective amount of [a purine analog or a pharmaceutical salt thereof] azathioprine, 6-mercaptopurine, 6-thioguanine nucleotide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

21. (Amended) The method of Claim 19, wherein said [purine analog is] formulation includes azathioprine or a [derivative] pharmaceutically acceptable salt thereof.

23. (Amended) The method of Claim [19] 21, wherein said azathioprine or a pharmaceutically acceptable salt thereof is in a solution or suspension at a concentration between 0.5 and 50 mg/ml.

24. (Amended) The method of Claim [19] 21, wherein said azathioprine or a pharmaceutically acceptable salt thereof is administered at a dosage between 50 and 250 mg/day.

25. (Amended) The method of Claim [19] 21, wherein said azathioprine or a pharmaceutically acceptable salt thereof is administered in a solution or a suspension.

26. (Amended) The method of Claim 19, wherein said [azathioprine or a pharmaceutically acceptable salt thereof] formulation is administered in the form of a member

selected from the group consisting of a lozenge, a lollipop, a pellet, a cream, a gel, an ointment, a quick dissolving tablet, gum, or a mucosal adhesive.

27. (Amended) The method of claim 19, wherein said step of topically contacting includes rinsing the mouth of said patient with said [effective amount of azathioprine or a pharmaceutically acceptable salt thereof] formulation for at least one minute; and

swallowing said [effective amount] formulation after said step of rinsing.

28. (Amended) The method of claim [19] 21, wherein said step of topically contacting includes rinsing said mouth with said [effective amount of azathioprine or a pharmaceutically acceptable salt thereof] formulation for at least one minute, and thereafter expectorating said [azathioprine] formulation without swallowing.

36. (Amended) The method of claim 19, wherein said autoimmune disease of the mouth is lichenoid changes and aphthae associated with acquired immune deficiency syndrome ((AIDS)).